Appendix B. History of the multi-stage model of carcinogenesis

The incidence rate of many carcinomas rises rapidly in old age, according to the mathematical relationship

$$rate \propto (age)^K$$

where K usually lies between five and six.[1] Based on a proposal by Nordling[2] that the malignant transformation of a cell was a result of successive mutations, Armitage and Doll[3] proposed a mathematical model of carcinogenesis in which a cell must go through a sequence of changes before becoming malignant. This model reproduces the above age-incidence profile with exponent K if a cell must go through $K+1$ steps before malignant transformation.

The multi-stage model was adapted to other cancers that do not show the same age-incidence profile by substituting another time scale for age. Doll[4] showed that lung cancer in smokers fits the multi-stage model when duration of smoking is used in place of age. Pike et al.[5] fitted breast cancer into the multi-stage framework by introducing a synthetic "breast tissue age" that begins at puberty and whose rate of change relative to physical age is mediated by other hormonal events such as pregnancy and menopause.

Despite these advances, further elaboration of the multi-stage model of carcinogenesis from epidemiological data was not possible. It became clear that a wide variety of different mechanistic models predict the same pattern of incidence rates.[6] It was therefore impossible to draw detailed mechanistic conclusions from the

incidence profile of a cancer. Nevertheless, there have been two important contributions of the multi-stage model to understanding cancer aetiology. Firstly, the theory that a cell must undergo a certain number of mutations in order to become malignant has been largely vindicated by advances in molecular biology.[7] Hanahan and Weinberg[8] presented a modern interpretation of the theory of multistage carcinogenesis in which cancer is considered a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth. Secondly, in cancers with a predominant risk factor, the best predictor of risk is duration of exposure, rather than age *per se.*[9,10]

In 2004, on the 50th anniversary of its publication, Armitage and Doll's article was reprinted as a discussion paper. [11]

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